REMARKS

Upon entry of the instant amendment, claims 2, 13, 14, 18-20, 23, 24, 26-30, 32, 33, and 36-45 constitute the pending claims in the present application. Claims 7, 8, 10-12, 15-17, 21, 22, 25, 31, 34, and 35 are canceled without prejudice. Applicants reserve the right to prosecute claims of similar or identical scope in future applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim rejections under 35 U.S.C. 112, second paragraph

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Particularly, the Office Action asserts that Claim 16 lacks antecedent basis.

To expedite prosecution, Applicants have amended Claim 2 and canceled a few dependant claims, including Claim 16, without prejudice. Applicants reserve the rights to prosecute claims of similar or identical scope in future applications. Rejection to Claim 16 is rendered moot. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph – written description

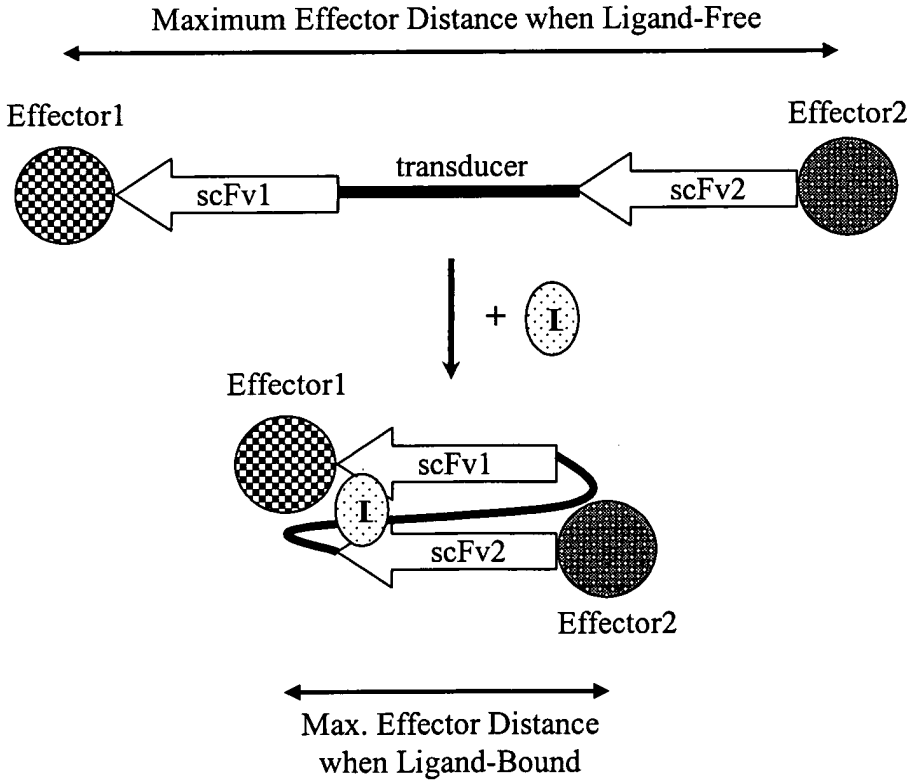
Claims 2, 7, 8, and 10-45 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Office Action asserts that the claimed genus broadly encompasses any pair of single chain antibodies (scFv) capable of recognizing any ligand, coupled to any effector and any transducer, such that one skilled in the art cannot recognize that Applicants have possession of what is claimed. The thrust of the Office Action argument seems to be that, the "allosteric properties of the vast majority of molecular recognition elements (MREs) and transducers... are unknown, and ...the nature of the allosteric modification required to obtain a detectable change" in effector activity is "distinct," "complex and unpredictable, ... one skilled

in the art cannot possibly visualize or recognize the generic MMC of (the claimed invention)," because "the description fails to teach how the component parts can be assembled to provide the function recited in the claims."

Applicants have amended Claim 2 and several dependent claims to further clarify the subject matter claimed. Support can be found, for example, on page 21, last 3 paragraphs. Amended Claim 2 clearly sets forth the specific order of the various MMC components, with no reasonable alternative interpretation. Thus a skilled artisan would readily understand and envision the specific structure of the claimed MMC.

Regarding the allosteric property, Applicants submit that, at least in the claimed invention, the nature of such allosteric property is relatively straight forward and rather predictable. This is partly because scFv has well-characterized structure, such that "in the ligand-free state, ...portions of the single chain antibody domain distal from the ligand binding site are physically separated. Ligand binding drives the ligand binding site into its preferred, 'natural' conformation such that the distal ends of the single chain antibody domains are juxtaposed." (the paragraph bridging pages 21 and 22, emphasis added). Also see Figures 1, 5, and 6. The following schematic diagram may help to illustrate the point.



It is apparent that, in the above diagram, the maximum distance between the two MMC effectors (at the N- and C- termini of the MMC, respectively) is much larger (*e.g.*, at least *twice*, may be *three times* or more in the full-extended state depending on transducer length) in the ligand-free state than in the ligand-bound state. This is consistent with the data shown in Fig. 5 and 6, where ~89 Å separates the two effectors when the MMC is ligand-free, and the distance becomes ~40 Å when the two scFv's come together to bind a ligand (*e.g.*, antigen).

Apparently, when there is no ligand binding, the transducer linking the two scFv's may be fully extended, and the two scFv's may only be loosely associated with each other, if at all. As a result, the two effectors situated at the two ends of the MMC molecule tend to be farther apart from each other. However, when a ligand binds to the two scFv's, the conformation of the MMC is much more compact and constrained, partly depending on the transducer length. The two scFv's must come together to form a stable binding pocket for ligand binding. This *necessarily* creates a much compact and taut MMC-ligand complex, and *necessarily* brings the two effectors to juxtapose positions. (see diagram above, and compare Figures 5 and 6).

It should be noted that the transducer in the claimed invention need not contribute to the conformation change. It may simply "permit" the two scFv's to come together and form a ligand-binding pocket (see page 12, line 14). Thus even a random polypeptide of suitable length (for example, ~20 amino acids) may constitute the transducer of the invention.

In addition, despite the potential mild sequence variations among different scFv's, their three-dimensional fold is pretty conserved. The major difference between different scFv domains probably resides in the three Ag-recognizing CDR (Complementarity Determining Region) regions on each scFv domain. These CDRs are merely a few amino acids long each, and usually do not have significant effects on the overall compact structure of the MMC, when the two scFv domains come together to bind an Ag. In other words, a skilled artisan could readily envision that different scFv's, even having different ligand specificity, will predictably produce substantially the same conformation change (*e.g.*, the two effectors come to juxtapose positions) when binding to their respective antigen ligands.

Furthermore, amended Claim 2 recites fluorescent effectors, which are well-characterized themselves. The specification also provides ample description regarding the types of fluorophores that may be used in the claimed invention, the mechanisms of fluorescent change,

and methods to calculate the efficiency of FRET, etc. (see pages 13-20). A skilled artisan could readily envision that Applicants have possession of the claimed embodiments using fluorophores other than YFP and CFP.

In summary, at least regarding the presently claimed invention, the relevant allosteric properties are relatively straight forward and fairly predictable. In view of the well-characterized structure of the scFv's, their quite conserved 3-D folding, Applicants have adequately described the claimed genus of MMC. A skilled artisan, in view of such description, could readily envision various species MMCs within the scope of the claimed genus, since the various described species in the application is representative of other species not expressly described.

For the reasons presented above, Applicants submit that all pending claims as amended fully comply with the written description requirement. Accordingly, reconsideration and withdrawal of written description requirement rejection under 35 U.S.C. 112, first paragraph are respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph - enablement

Claims 2, 7, 8, and 10-45 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while allegedly being enabling for a molecular clasp comprising a single chain Ab 1LMK or 1A14 comprising YFP and CFP effector molecules, allegedly does not reasonably provide enablement for the broad scope of any molecular recognition element, and effector and a transducer. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants have amended Claim 2 and several dependent claims to further clarify the subject matter claimed.

As argued above, amended Claim 2 recites a specific MMC general structure encompassing specific classes of effectors (*i.e.*, fluorophores) and MRE (*i.e.*, scFv). In view of the well-characterized nature of the scFv's and the fluorophores, and the well-conserved three-dimensional folding of scFv, Applicants have taught a skilled artisan how to make and use the claimed MMC without undue experimentation.

The Office Action first argues that large scale screening is "well above what is ordinary," since the combined resources of large pharmaceutical companies make what is routine for them not routine for one of ordinary skill in the art. Applicants respectfully disagree.

MPEP 2141.03 states: "'[f]actors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.' *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984)." None of these factors relate to the environment or facility in which the skilled artisan works, nor the type / amount of resources he has access to. In other words, the skill of an imaginary artisan of ordinary skill does not diminish simply because he works by himself, nor does it increase because he works for a large pharmaceutical company with large funding. The imaginary artisan is deemed to have access to all resources and state-of-the-art technology available at the time of filing.

The Office Action also cites Marvin and Brennan to support the non-enablement argument. Marvin merely stressed that each biosensor is unique and requires substantial development time, but it also acknowledged that biosensors have been successfully developed. The claimed MMC does contain unique designs using specific types of effectors and MREs. Marvin does not *per se* contradict the enablement of the claimed invention.

Brennan relates to design of artificial enzymes which activity can be regulated by ligand binding. However, this is not the subject matter claimed. In contrast, the scFv technology is a mature technology that has been routinely used at the time of filing of the instant application. Numerous studies have confirmed that the binding affinity by scFv approximates (if not equals) that of the original monoclonal Ab from which the scFv is derived. Thus Brennan is not probative of the issue at hand.

The Office Action also asserts that due to the high degree of unpredictability, a skilled artisan would need undue experimentation to differentiate operable and inoperable embodiments. Based on the arguments presented above, Applicants submit that the degree of predictability is high regarding the presently claimed invention. Ligand (Ag) binding to scFv *necessarily* induces the requisite conformation change that brings about a more compact MMC. Such high degree of

predictability partly stems from the fact that scFv is a highly mature technology, and that scFv retains the conserved 3-D folding of the antibody variable domains.

Therefore, Applicants submit that the specification has provided ample working examples that reasonably correlates with the full scope of the claimed invention. A skilled artisan would be able to practice the claimed invention without undue experimentation. Thus, the enablement requirement of 35 U.S.C. 112, first paragraph is met. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

Date: January 17, 2006

Yu Lu, Ph.D.
Reg. No. 50,306

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050